REMARKS

The title has been amended to reflect that the claims are directed to compositions and methods relating to the fchd605 gene in particular.

In addition, a minor editorial error has been corrected at page 118, lines 35-36. Specifically, the references to turbulent and laminar shear stress were inadvertently reversed in this passage summarizing the results reported in Section 7.2. Support for the accurate description of the down-regulation of fchd545 under turbulent shear stress, as compared to laminar shear stress and the control can be found in Section 7.2 at page 121, lines 34-36.

Claims 70, 71, 74, and 77-102 are currently pending. Claims 72, 73, 75 and 76 have been canceled without prejudice to Applicant's right to pursue the subject matter of these claims in this or additional applications. Claims 70, 71, 74, and 77-89, as well as new claims 97-102, drawn to the elected subject matter, are under active consideration. The claims have been amended, and new Claims 97-102 have been added, to more particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The amendments to the claims are completely supported by the specification. No new matter has been introduced.

More specifically, Claims 70, 71, and 74 have been amended to specify that the claimed polynucleotides cover both single and double stranded molecules, as indicated, for example, in the sequence listing (strandedness is "both"), and in accordance with 37 C.F.R. § 1.822(j) and M.P.E.P. § 2423.03, which specify that double stranded nucleotide sequences are represented in the sequence listing by a single strand. Support for the amendment can be found, for example, in the specification at page 24, lines 22-28; page 34, lines 18-26; page 37, lines 18-30 and page 38, lines 14-17 and 33-36.

The dependency of Claims 77 and 80-85 has been amended to reflect the addition of new Claims 97-99.

Claims 84-87 have been amended to specify that the cells are cultured. Support for such cells being cultured can be found, for example, in the specification at Sections 5.1.1.1 through 5.1.1.6 at pages 16-20, and at page 108, lines 31-35.

Support for new Claims 101 and 102, with respect to the specified strands, can be found, for example, at page 22, lines 10-21 and 27-29 of the specification.

A. Restriction Requirement Pursuant To 35 U.S.C. § 121

The Examiner has required restriction of the claims into two groups, Group I (Claims 70-89) and Group II (Claims 90-96), contending that each is directed to an independent and distinct invention (Office Action dated May 11, 1998, hereinafter "Office Action"). Claims 72, 73, 75 and 76 have been canceled, without prejudice, for the purpose of expediting prosecution of the instant application. Applicant hereby confirms the telephonic election made on May 1, 1998, with traverse, to prosecute the remaining subject matter of Group I, Claims 70, 71, 74 and 77-89, as well as new Claims 97-102, drawn to isolated polynucleotides, vectors and genetically engineered host cells containing the polynucleotides, and methods of producing polypeptides encoded by the polynucleotides.

Applicant respectfully requests that the Examiner withdraw the restriction requirement so that Groups I and II are examined together. Specifically, the claims in these groups are all drawn to isolated polynucleotides, vectors and genetically engineered host cells containing the polynucleotides, methods of producing polypeptides encoded by the polynucleotides and to isolated polypeptides which are encoded by the polynucleotides. Indeed, were Applicant to elect Group I (concerning isolated polynucleotides, vectors and genetically engineered host cells containing the polynucleotides, and methods of producing polypeptides encoded by the polynucleotides), the required search would necessarily encompass that for the subject matter of Group II (concerning the isolated polypeptides which are encoded by the polynucleotides).

The M.P.E.P. § 803 states:

> If the search and examination of an entire application can be made without serious burden, the examiner >must< examine it on the merits, even though it includes claims to distinct or independent inventions (emphasis added).

Thus, in view of M.P.E.P. § 803, all the subject matter in Groups I and II should be examined together. Even if the subject matter of these groups are distinct inventions, it would not be a "serious burden" on the Examiner to search these groups in this application. Indeed, as Applicant has explained above, the burden of searching these groups together would be no greater than that for Group I alone.

In summary, Applicant has demonstrated that the subject matter of the claims of Groups I and II should be examined in the same application. Applicant requests, therefore, that the restriction requirement be withdrawn and that all of Claims 70, 71, 74 and 77-102 be searched and examined together.

Applicant retains the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

B. The Claims Are Directed To Patentable Subject Matter Under 35 U.S.C. § 101

Claims 84-87 are rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. The rejection has been obviated in view of the amendment to Claims 84-87, specifying that the genetically engineered host cells are "cultured". Hence, Applicant respectfully requests that the rejection under Section 101 be withdrawn.

C. The Claimed Subject Matter Is Enabled Under 35 U.S.C. § 112, First Paragraph

Claims 70-89 are rejected under 35 U.S.C. §112, first paragraph, on the ground that the specification does not provide sufficient disclosure to enable the use of the claimed polynucleotides. The rejection of Claims 72, 73, 75 and 76 is moot, in view of the

cancellation of the claims. The rejection of Claims 70, 71, 74 and 77-89 is respectfully traversed.

This rejection is apparently predicated on the assertion that a person of ordinary skill in the art would have to know the biological function of the polypeptide encoded by each claimed polynucleotide in order to be able to use the claimed polynucleotides. *See*, Office Action, at page 5, lines 10-12.

In contrast to the Examiner's assertion, however, Applicant emphasizes that the biological function of the encoded polypeptide and its specific physiological role in cardiovascular disease is not required for use of the claimed polynucleotides.

A disclosed utility that supports the patentability of the claimed compositions is use as a probe. Such probes are useful for genetic mapping, as described in the specification. *See, for example*, page 31, lines 14-22.

A further disclosed utility of the claimed compositions is use as a diagnostic indicator of cardiovascular disease (*see, for example* Section 5.8.1). As noted by the Examiner, the fchd605 gene was up-regulated after 5 hours of treatment with oxidized LDL. *See*, Office Action at page 4. Applicant respectfully notes that the fchd605 gene expression is up-regulated under paradigm A, *i.e.* Foam Cell Paradigm - 1, and not under paradigm D, *i.e.* Endothelial Cell Shear Stress Paradigm, as indicated in the Office Action at page 5[1]. *See, for example*, the specification at page 16, line 30 to page 17, line 20; and Table 1 at page 36. The foam cell paradigm, as described in the specification, utilizes oxidized LDL treatment to analyze genes which are differentially expressed under conditions associated with foam cell development.

[1] The reference Papadaki *et al.*, 1997, Biotechnol. Prog. 13: 209-221, cited in the Office Action at page 6, therefore, does not apply to the claimed subject matter.

The Example presented in Section 6 of the specification demonstrates in detail the use of such a foam cell paradigm to identify genes which are differentially expressed in treated versus control cells. As detailed in the specification at page 2, lines 13-31, for example, foam cells are the major constituent of the fatty streak, a well known constituent of atherosclerotic plaques. Interactions between foam cells and the endothelial and SMCs which surround them lead to a state of chronic local inflammation which can eventually lead to smooth muscle cell proliferation and migration, and the formation of a fibrous plaque. Thus, the polynucleotides of the claimed invention are also useful, for example, as indicators of foam cell differentiation and foam cell formation which lead to atherosclerosis (*see, for example* Section 5.8.1) .

In the Office Action, the Examiner also asserts that the specification is not enabling for determining the specificity of hybridization under "moderately stringent conditions" and/or "highly stringent conditions" to the polynucleotides encoding Seq ID NO:10 (*see*, Office Action at page 7). To the contrary, Applicant respectfully invites the Examiner's attention to the specification at page 37, line 25 to page 38, line 24, where highly stringent and moderately stringent hybridization conditions, for using the claimed polynucleotides as probes, for example, are described in detail.

In summary, the specification describes in detail the use of the claimed polynucleotides as probes in chromosomal mapping and as indicators of foam cell formation and development, for example. Such use does not require identification of the biological function of the claimed polynucleotides. Furthermore, the specification describes in detail the specified hybridization conditions for carrying out the use of the claimed polynucleotides as probes. In view of the above, therefore, Applicant submits that the specification fully enables the use of the claimed invention, without requiring undue experimentation. Accordingly, Applicant respectfully requests that the rejection under § 112, first paragraph, be withdrawn.

D. The Claims Are Definite Under 35 U.S.C. § 112, Second Paragraph

Claims 70-89 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

More specifically, the Examiner rejected Claims 70, 71, 74, and claims dependent thereto, for being indefinite in the recitation of "which is the complement of (a)". This rejection has been obviated by the amendment to the claims deleting this phrase. As noted above, these claims as amended specify that the claimed polynucleotides cover both single and double stranded molecules, as indicated, for example, in the sequence listing (strandedness is "both"), and in accordance with 37 C.F.R. § 1.822(j) and M.P.E.P. 2423.03, which specify that double stranded nucleotide sequences are represented in the sequence listing by a single strand. Such double stranded and single stranded polynucleotides can be used as probes, as discussed above in connection with the rejection under 35 U.S.C. § 112, first paragraph..

The rejection of Claims 84-87 under § 112, second paragraph, with respect to the phrase "a genetically engineered host cell" has been obviated by the amendment to these claims specifying that the cells are "cultured".

The rejection of Claims 84-87 with respect to the phrase "exogenous to the polynucleotide" has been obviated by the deletion of this phrase from the respective claims.

Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

E. The Rejections Of Claims 72, 73 and 75-89 Under 35 U.S.C. § 102(a)

Claims 72, 73 and 75-89 are rejected under 35 U.S.C. § 102(a) as being anticipated, or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over The WashU-Merck

EST Project ("WUM-N32077").[2] The rejection of Claims 72, 73, 75 and 76 is obviated in view of the cancellation of the claims. The rejection of Claims 77-89 is respectfully traversed.

Specifically, the Examiner contends that WUM-N32077 describes a polynucleotide sequence isolated from a cDNA clone which is 96.4% identical to a DNA segment consisting of residues 5-550 of SEQ ID NO:9. To the contrary, the sequence disclosed in WUM-N32077 corresponds to residues number 658-1204, and not residues 5-550 of SEQ ID NO:9. As clearly depicted in SEQ ID NO:9 (*see also* Figure 5), residues 658-1204 correspond to the 3'-untranslated region of the polynucleotide, and not to any of the polypeptide coding region.

Applicant notes that Claims 77-89 now depend on Claims 70, 71, 74, and 97-99, and not Claims 72, 73, 75 or 76, which are now canceled. Furthermore, Claims 77-89 are directed to polynucleotides of the fchd605 polypeptide coding region. Therefore, the sequences of WUM-N32077 cited by the Examiner, which correspond to 3'-untranslated region, neither anticipate nor make obvious the claimed polynucleotides. Thus, Applicant respectfully requests that this rejection under § 102(a), or in the alternative, under § 103(a) over WUM-N32077 be withdrawn.

F. The Rejections Of Claims 72, 73 And 75-89 Under 35 U.S.C. §§ 102(b) Or 103

Claims 72, 73 and 75-89 are rejected under 35 U.S.C. §102(b) as being anticipated, or in the alternative, under 35 U.S.C. §103 as being unpatentable over The WashU-Merck EST Project ("WUM-T49532").[3] The rejection of Claims 72, 73, 75 and 76 is moot in view of the cancellation of the claims. The rejection of Claims 77-89 is respectfully traversed.

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[2] published January 10, 1996, AN:N32077, embl-est Database.

[3] published February 8, 1995, AN:T49532, embl-est Database.

The Examiner contends that WUM-T49532 teaches a polynucleotide sequence isolated from a cDNA clone which is 96.3% identical to a DNA segment consisting of residues 1-403 of SEQ ID NO:9. To the contrary, the sequence disclosed in WUM-T49532 corresponds to residues number 788-1184, and not residues 1-403, of SEQ ID NO:9. As clearly depicted in SEQ ID NO:9, residues 778-1184 correspond to 3'-untranslated region of the polynucleotide, and not for any of the coding sequence. As discussed above in connection with the rejection over WUM-N32077, Claims 77-89 now depend from Claims 70, 71, 74, and 97-99, and not from Claims 72, 73, 75 or 76, which are now canceled. Furthermore, Claims 77-89 relate to polynucleotide sequences of the fchd605 polypeptide coding region. Therefore, the sequences of WUM-T49532 cited by the Examiner, which correspond to 3'-untranslated region, neither anticipate nor make obvious the claimed polynucleotides. Thus, Applicant respectfully requests that this rejection under § 102(a), or in the alternative, under § 103(a) over WUM-T49532 be withdrawn.

G. The Rejection Of Claims 70 and 72-89 Under 35 U.S.C. §103(a)

Claims 70 and 72-89 are rejected under 35 U.S.C. §103(a) based on Hillier *et al.* Swiss-prot35 Database, AC:P46695 ("Hillier"), taken in view of Fuller *et al.*, 1996, Seminars in Oncology, 23:4-21 ("Fuller"). The rejection of Claims 72, 73, 75 and 76 is moot in view of the cancellation of the claims. The rejection of Claims 70, 74 and 77-89 is respectfully traversed.

The Examiner contends that the Hillier amino acid sequence at P46695 is 98.9% identical to the amino acid sequence of SEQ ID NO:10. The Examiner further contends that Fuller, for example, teaches DNA recombinant techniques that can be used to construct polynucleotide sequences encoding gene products, such as that disclosed in Hillier, and thus, that it would have been obvious for one of ordinary skill in the art to employ DNA

recombinant techniques to construct DNA sequences encoding the polypeptide of Hillier. *See*, Office Action at page 12.

The Examiner also asserts that the P46695 amino acid sequence of Hillier was published in February, 1995. In contrast to the Examiner's assertion, Applicant submits herewith documentary evidence which clearly indicates that the complete amino acid sequence of Hillier was not published until February, 1998. More specifically, Applicant submits herewith, as Exhibit A, a copy of a National Center for Biotechnology Information (NCBI) data base report detailing the Hillier sequence published in February, 1995. As the report at Exhibit A clearly indicates, only an expressed sequence tag (EST) corresponding to a 329 base pair partial nucleotide sequence was described in the report dated February 6, 1995. Furthermore, as noted in the sequence, numerous nucleotides are designated as "n", and, thus, the precise nucleotide sequence of this EST was not completely identified.

The amino acid sequence corresponding to the partial nucleotide sequence set forth at Exhibit A was reported on November 1, 1995 and assigned locus number 1169902. A copy of the NCBI data base report summarizing Locus number 1169902 is attached hereto as Exhibit B. As Exhibit B clearly shows, the amino acid sequence reported on November 1, 1995 is a 106 amino acid partial sequence. This partial amino acid sequence, similar to the nucleotide sequence at Exhibit A, consists of numerous uncertainties, as noted by the amino acids marked as "x". Applicant notes that the Comment entry of this report states "On October 9, 1997, this sequence was replaced by a new version gi:2507034". This report indicates, therefore, that the 1169902 partial sequence remained in the data base until October 9, 1997.

Applicant submits herewith as Exhibit C a copy of the NCBI data base report for the aforementioned Locus number 2507034 containing the complete 156 amino acid sequence for to IEX-1. Applicant notes that the Comment entry of this report states "On October 9, 1997,

this sequence version replaced gi:1169902", which is the number assigned to the 106 partial amino acid sequence set forth in Exhibit B. Furthermore, Applicant notes that this data base record has the report date of February 1, 1998. Thus, according to the data base records, the complete 156 amino acid sequence that was deposited by Hillier et al. with data base, as cited by the Examiner, was not made available to the public until February 1, 1998. Thus, although Hillier eventually disclosed a sequence which is 98.9% homologous to SEQ ID NO:10, a careful examination of the data base historical record clearly indicates that this sequence was provided by Hillier et al. to the data base until after the February 13, 1997 filing date of the instant application.

Therefore, it would not have been obvious, at the time of the invention, to use the partial nucleotide sequence disclosed by Hillier on February 1, 1995, or the partial amino acid sequence disclosed on November 1, 1995, to construct the claimed polynucleotides. This is especially true in view of the fact that numerous inconsistencies exist between the sequences disclosed by Hillier in 1995 (both nucleotide and amino acid) and the complete sequence which was relied upon by the Examiner that was finally disclosed by Hillier in 1998.

Applicant respectfully requests, therefore, that the rejection under 35 U.S.C. § 103 based on the sequences cited by the Examiner in Hillier be withdrawn.

SUMMARY

Applicant respectfully requests the entry of the foregoing amendments and remarks into the file of the above-captioned application. Applicant believes that each ground for rejection or objection has been successfully overcome or obviated and that the application is in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application is earnestly requested.

Respectfully submitted,

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Appendix - Pending Claims

70. (amended) An isolated polynucleotide comprising a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO:10.

71. (amended) An isolated polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO:9.

74. (amended) An isolated polynucleotide comprising the nucleotide sequence of the polypeptide coding region set forth from nucleotide residue number 1 to 468 of SEQ ID NO:9.

77. (amended) The isolated polynucleotide of Claim 70, 71, 74, 97, 98, or 99 which is DNA.

78. The isolated polynucleotide of Claim 77 which is cDNA.

79. The isolated polynucleotide of Claim 77 which is genomic DNA.

80. (amended) The isolated polynucleotide of Claim 70, 71, 74, 97, 98, or 99 which is RNA.

81. (amended) The isolated polynucleotide of Claim 70, 71, 74, 97, 98, or 99 which further comprises a label.

82. (amended) A polynucleotide vector containing the polynucleotide of Claim 70, 71, 74, 97, 98, or 99.

83. (amended) An expression vector containing the polynucleotide of Claim 70, 71, 74, 97, 98, or 99 in operative association with a nucleotide regulatory element which controls expression of the polynucleotide in a host cell.

84. (amended) A cultured genetically engineered host cell containing the polynucleotide of Claim 70, 71, 74, 97, 98, or 99.

85. (amended) A cultured genetically engineered host cell containing the polynucleotide of Claim 70, 71, 74, 97, 98, or 99 in operative association with a nucleotide regulatory element that controls expression of the polynucleotide in the host cell.

86. (amended) The cultured genetically engineered host cell of Claim 85 which is prokaryotic.

87. (amended) The cultured genetically engineered host cell of Claim 85 which is eukaryotic.

88. A method of producing a polypeptide fchd605 gene product, comprising the steps of:

(a) growing the genetically engineered host cell of Claim 86 in a culture; and

(b) collecting the polypeptide gene product from the culture.

89. A method of producing a polypeptide fchd605 gene product, comprising the steps of:

(a) growing the genetically engineered host cell of Claim 87 in a culture; and

(b) collecting the polypeptide gene product from the culture.

90. An isolated polypeptide having the fchd605 amino acid sequence set forth in SEQ ID NO:10.

91. An isolated polypeptide encoded by a polynucleotide which hybridizes under highly stringent conditions to the complement of the fchd605 nucleotide sequence set forth in SEQ ID NO:9.

92. An isolated polypeptide encoded by a polynucleotide which hybridizes under moderately stringent conditions to the complement of the fchd605 nucleotide sequence set forth in SEQ ID NO:9, wherein the polynucleotide is differentially expressed in a cardiovascular disease state.

93. The polypeptide of Claim 91 or 92 wherein the polypeptide contains the amino acid sequence set forth in SEQ ID NO:10.

94. An isolated polypeptide encoded by a polynucleotide which hybridizes under highly stringent conditions to the complement of the fchd605 polypeptide coding region, as set forth from nucleotide residue number 1 to 468 of SEQ ID NO:9.

95. An isolated polypeptide encoded by a polynucleotide which hybridizes under moderately stringent conditions to the complement of the fchd605 polypeptide coding region, as set forth from nucleotide residue number 1 to 468 of SEQ ID NO:9, wherein the polynucleotide is differentially expressed in a cardiovascular disease state.

96. The polypeptide of Claim 94 or 95 wherein the polypeptide contains the amino acid sequence set forth in SEQ ID NO:10.

97. (new) An isolated polynucleotide consisting of a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO:10.

98. (new) An isolated polynucleotide consisting of the nucleotide sequence of the polypeptide coding region set forth from nucleotide residue number 1 to 468 of SEQ ID NO:9.

99. (new) An isolated polynucleotide consisting of the nucleotide sequence set forth in SEQ ID NO:9.

100. (new) The isolated polynucleotide of Claim 70, 71, 74, 97, 98, or 99 which is double stranded.

101. (new) The isolated polynucleotide of Claim 70, 71, 74, 97, 98, or 99 which is the coding strand.

102 (new) The isolated polynucleotide of Claim 70, 71, 74, 97, 98, or 99 which is the non-coding strand.